Stedman's Dictionary
Define:
Search

Document Outline
- Warnings
- Description
- Clinical Pharmacology
- Indications and Usage
- Dosage and Administration
- Contraindications
- Warnings (2)
- Precautions
- Drug Interactions
- Adverse Reactions
- Overdosage
- How Supplied
- References
- How Supplied (2)

PDR® entry for

INTRON® A (Schering)
Interferon alfa-2b,
recombinant
For Injection

WARNING

Alpha interferons, including INTRON® A, cause or aggravate fatal or li autoimmune, ischemic, and infectious disorders. Patients should be mon and laboratory evaluations. Patients with persistently severe or worsenin conditions should be withdrawn from therapy. In many but not all cases INTRON A therapy. See **WARNINGS** and **ADVERSE REACTIONS**

(*back to top*)

DESCRIPTION

INTRON A Interferon alfa-2b, recombinant for intramuscular, subcuta interferon product.

Interferon alfa-2b, recombinant for Injection has been classified as an daltons produced by recombinant DNA techniques. It is obtained from engineered plasmid containing an interferon alfa-2b gene from huma containing the antibiotic tetracycline hydrochloride at a concentration product. The specific activity of Interferon alfa-2b, recombinant is app

		Pow
Vial Strength	**mL Diluent**	**Final Conce after Recons million IU/**
3 MIU	1	3
5 MIU	1	5
10 MIU	2	5
18 MIU	1	18
25 MIU	5	5
50 MIU	1	50
*Each mL also contains 20 mg glyci sodium phosphate monobasic, and 1		
† Based on the specific activity of ap measured by HPLC assay.		
++ The 10 MIU vial for intralesional provided diluent.		

Prior to administration, the INTRON A Powder for Injection is to be re recombinant for Injection (bacteriostatic water for injection) containin **ADMINISTRATION**) INTRON A Powder for Injection is a white to cr

Solution

Vial Strength	Final Concentration *
3 MIU	3 million IU/0.5 mL
5 MIU	5 million IU/0.5 mL
10 MIU	10 million IU/1.0 mL
18 ‡MIU multidose	3 million IU/0.5 mL
25 ¶MIU multidose	5 million IU/0.5 mL

*Each mL contains 7.5 mg sodium c mg sodium phosphate monobasic, 0. and 1.5 mg m-cresol as a preservativ

† Based on the specific activity of ap measured by HPLC assay.

‡ This is a multidose vial which cont alfa-2b, recombinant per 3.8 mL in o each containing 3 million IU of INT Injection (for a label strength of 18 m

¶ This is a multidose vial which cont alfa-2b, recombinant per 3.2 mL in o doses, each containing 5 million IU for Injection (for a label strength of 2

Solution in Mu

Pen Strength	**Final Concentration ***	**INTR D (6 do**
18 MIU	22.5 MIU/1.5 mL	3 M
30 MIU	37.5 MIU/1.5 mL	5 M
60 MIU	75 MIU/1.5 mL	10

*Each mL also contains 7.5 mg sodi 1.3 mg sodium phosphate monobasi 80, and 1.5 mg m-cresol as a preserv

† Based on the specific activity of ap measured by HPLC assay.

These packages do not require reconstitution prior to administration (

clear, colorless solution.

(*back to top*)

CLINICAL PHARMACOLOGY

General The interferons are a family of naturally occurring small pr 27,600 daltons produced and secreted by cells in response to viral inf

Preclinical Pharmacology Interferons exert their cellular activities by cell membrane, interferons initiate a complex sequence of intracellula certain enzymes, suppression of cell proliferation, immunomodulating augmentation of the specific cytotoxicity of lymphocytes for target ce

In a study using human hepatoblastoma cell line, HB 611, the *in vitro* B virus (HBV) replication.

The correlation between these *in vitro* data and the clinical results is effects.

Pharmacokinetics The pharmacokinetics of INTRON A Interferon alfa following single doses of 5 million IU/m ^{2} administered intramuscular design.

The mean serum INTRON A concentrations following intramuscular an concentrations obtained via these routes were approximately 18 to 11 half-life of INTRON A Interferon alfa-2b, recombinant for Injection fol hours. Serum concentrations were undetectable by 16 hours after the

After intravenous administration, serum INTRON A concentrations pe slightly more rapid rate than after intramuscular or subcutaneous dru elimination half-life was approximately 2 hours.

Urine INTRON A concentrations following a single dose (5 million IU/m This result was expected since preliminary studies with isolated and p interferon catabolism.

There are no pharmacokinetic data available for the intralesional rout

Serum Neutralizing Antibodies In INTRON A treated patients tested were detected in 0% (0/90) of patients with hairy cell leukemia, 0.8% (1/24) of patients with AIDS-Related Kaposi's Sarcoma. Serum neutr INTRON A doses in malignancies other than hairy cell leukemia or AID serum anti-interferon neutralizing activity in these indications is not k

Serum anti-interferon neutralizing antibodies were detected in 7% (1 treatment with 3 million IU TIW of INTRON A therapy for chronic hep hepatitis B at 5 million IU QD for 4 months, and in 3% (1/33) of patie were detected in 9% (5/53) of pediatric patients who received INTRO hepatitis B or C patients, pediatric and adults with detectable serum n

Hairy Cell Leukemia In clinical trials in patients with hairy cell leuk INTRON A treatment, resulting in reduced numbers of circulating red nonsplenectomized patients achieved substantial and sustained impro patients and at least some improvement (minor responses) occurred hypercellularity and hairy cell infiltrates. The hairy cell index (HCI), w cell infiltrate, was >/=50% at the beginning of the study in 87% of p

months and to 14% after 1 year. These results indicate that even tho treatment may be required to obtain maximal reduction in tumor cell

The percentage of patients with hairy cell leukemia who required red the percentage of patients with confirmed and serious infections decli significant hypersplenism was demonstrated in some patients.

A study was conducted to assess the effects of extended INTRON A tr this study, 126 responding patients were randomized to receive addit after 12 months of initial INTRON A therapy. During this 6-month per (11/60) who were not treated. This represents a significant difference Rank/Wilcoxon). Since a small proportion of the total population had similar pattern in relapses was seen when all randomized treatment, 15% (10/66) relapses among INTRON A patients occurred over a sign (p=0.0002/0.0001, Log Rank/Wilcoxon). Median time to relapse was group but could not be estimated in the INTRON A group.

Subsequent follow-up with a median time of approximately 40 month group followed for 24 months, overall median survival was approxima

Malignant Melanoma The safety and efficacy of INTRON A Interfero treatment in patients with melanoma who were free of disease (posts lesions of Breslow thickness >4 mm, or patients with lesions of any B controlled trial in 280 patients, 143 patients received INTRON A thera phase) followed by 10 million IU/m ^{2} subcutaneously three times per

INTRON A therapy produced a significant increase in relapse-free and observation patients was 1.72 years vs 0.98 years (p<0.01, stratified Kaplan-Meier method, was 37% for INTRON A treated patients vs 26% patients vs observation patients was 3.82 years vs 2.78 years (p=0.0 Kaplan-Meier method, was 46% for INTRON A treated patients vs 37%

In a second study of 642 resected high-risk melanoma patients, subje therapy for 1 year (same schedule as above), low-dose INTRON A the trial, high-dose INTRON A therapy demonstrated an improvement in years, p=not significant). Relapse-free survival in the low-dose INTRO low-dose INTRON A therapy showed a benefit in overall survival as co

Follicular Lymphoma The safety and efficacy of INTRON A in conju treatment in patients with clinically aggressive, large tumor burden, S by the presence of any one of the following: a nodal or extranodal tum (each with a diameter of >3 cm); systemic symptoms; splenomegaly leukemia.

In a randomized, controlled trial, 130 patients received CHVP therapy subcutaneously three times weekly for the duration of 18 months. CH mg/m ^{2}, and teniposide (VM-26) 60 mg/m ^{2}, administered intraveno 1 to 5. Treatment consisted of six CHVP cycles administered monthly, Patients in both treatment groups received a total of 12 CHVP cycles

The group receiving the combination of INTRON A therapy plus CHVP p=0.0001, Log Rank test). After a median follow-up of 6.1 years, the median survival for patients treated with CHVP plus INTRON A therap randomized, controlled studies of the addition of interferon alfa to an interferon alfa was associated with significantly prolonged progression

Condylomata Acuminata Condylomata acuminata (venereal or ge

The safety and efficacy of INTRON A Interferon alfa-2b, recombinant controlled double-blind clinical trials. In these studies, INTRON A dos (TIW), in

The patients were observed for up to 16 weeks after completion of th

INTRON A treatment of condylomata was significantly more effective and by an overall change in disease status. Of 192 INTRON A treated time of best response during the course of the study, 42% of INTRON Likewise, 24% of INTRON A patients vs 8% of placebo patients exper experienced moderate (>/=50% to

In one of these studies, 43% (54/125) of patients in whom multiple (

Patients who did not achieve total clearing of all their treated lesions second course of treatment, 38% to 67% of patients had clearing of a treated lesions after two courses of treatment ranged from 57% to 85

INTRON A treated lesions showed improvement within 2 to 4 weeks a therapy was noted 4 to 8 weeks after initiation of treatment.

The response to INTRON A therapy was better in patients who had co duration.

Another study involved 97 patients in whom three lesions were treate alfa-2b, recombinant for Injection per lesion followed by a topical app Treatment was given once a week for 3 weeks. The combined treatme was shown to be significantly more effective than podophyllin alone, difference in response was evident after the second treatment (Week best response, 67% (33/49) of the INTRON A Interferon alfa-2b, reco lesions clear while 42% (20/48) of the podophyllin treated patients h

AIDS-Related Kaposi's Sarcoma The safety and efficacy of INTRO Sarcoma (KS), a common manifestation of the Acquired Immune Def

In one study, INTRON A doses of 30 million IU/m ^{2} were administered Doses were adjusted for patient tolerance. The average weekly dose d averaged 110 million IU/week; and by 24 weeks averaged 75 million

Forty-four percent of asymptomatic patients responded vs 7% of sym and 1 month, respectively, for asymptomatic and symptomatic patien respectively, for the asymptomatic and symptomatic patients. Baselin

In another study, INTRON A doses of 35 million IU were administered other day dosing (QOD), was continued for up to 1 year in patients a months and the median duration of response was 5 months in the as

In all studies, the likelihood of response was greatest in patients with (interchangeable with T4 counts). Results at doses of 30 million IU/m together in TABLE 1. This table demonstrates the relationship of resp the 30 million IU/m ^{2} TIW and the 35 million IU/QD treatment groups

In the 30 million IU study group, 7% (5/72) of patients were complet million IU study had 13% (3/23 patients) complete responders and 1

For patients who received 30 million IU TIW, the median survival tim

	RESPONSE BY IN AIDS-RE 30 TIW, SC an
	Asympto
CD4<200	4/14
200 6/12	(50%)
CD4>400	5/7

*Data for CD4, and asympto were not available for all pat

Chronic Hepatitis C The safety and efficacy of INTRON A Interferon evaluated in 5 randomized clinical studies in which an INTRON A dose were placebo-controlled trials that evaluated a 6-month (24 week) co reduction in serum alanine aminotransferase (ALT) in a greater propo 6 months of follow-up, approximately 50% of the patients who respo pretreatment and posttreatment liver biopsies revealed histological im patients compared to controls.

Two additional studies have investigated longer treatment durations (treatment had hepatitis with or without cirrhosis in the absence of de normalization of the final two serum ALT levels during the treatment the treatment period with sustained normal ALT values lasting at leas

In Study 1, all patients were initially treated with INTRON A 3 million the initial 24-week treatment period were then randomly assigned to weeks. In Study 2, patients who met the entry criteria were randomly to receive INTRON A 3 million IU TIW subcutaneously for 96 weeks. I retrospective.

Results show that longer durations of INTRON A therapy improved th (CR) to INTRON A therapy after 6 months of treatment (149/352 [42 than if it was continued for 18 to 24 months (44/79 [56%]). Of all pa months of therapy was 22% and 26%, respectively, in the two trials. in significantly more responses, since almost all patients who respond

A subset (<50%) of patients from the combined extended dosing stu Improvement in necroinflammatory activity as assessed retrospective observed in both studies. A higher number of patients (58%, 45/78) 34/89) in this subset.

REBETRON® Combination Therapy containing INTRON A and REBETO in virologic load and improved histologic response in patients with co alone and in patients previously untreated with alfa interferon. See R

SUSTAINED ALT RESPON
*IN **CHRONIC***
INTRON
Treatment Grou

Study Number	*INTRON A 3 m IU 24 weeks treatmen*	
	ALT respons	
1	12/101	(12
2	9/67	(13
Combined Studies	**21/168**	**(12**
	ALT respons	
1	40/101	(40
2	32/67	(48

* Intent to treat groups.

† Study 1: 72 weeks of treatme

‡ Confidence intervals adjuste treatment arms in the study.

Chronic Hepatitis B ***Adults*** The safety and efficacy of INTRON A hepatitis B were evaluated in three clinical trials in which INTRON A d either 5 million IU daily (QD), or 10 million IU three times a week (TI compensated liver disease, and had chronic hepatitis B virus (HBV) in HBeAg positive). Patients were also serum HBV-DNA positive, an add patients had elevated serum alanine aminotransferase (ALT) and live the presence of antibody to human immunodeficiency virus (anti-HIV the studies.

Virologic response to treatment was defined in these studies as a loss parameters of response included loss of serum HBsAg, decreases in s

In each of two randomized controlled studies, a significantly greater p with untreated control patients (see TABLE 3). In a third study withou observed. Pretreatment with prednisone, evaluated in two of the stud

VIROLO
*IN **CHRONIC***
Treatment Grou

Study Number	*INTRON A 5 million IU QD*	
1 [7]	15/38	(39%)
2	--	--
3 [8]	--	--
All Studies	**15/38**	**(39%)**

*Loss of HBeAg and HBV D

† Patients pretreated with pred

‡ INTRON A treatment group

§ Untreated control patients ev
A subgroup subsequently rece
comparison is not applicable (

The response to INTRON A therapy was durable. No patient respondin relapsed during the follow-up period which ranged from 2 to 6 month in 100% of 19 responding patients followed for 3.5 to 36 months afte

In a proportion of responding patients, loss of HBeAg was followed by INTRON A therapy at a dose of 5 million IU QD, and 35% (8/23) of pa HBsAg in these studies.

In an ongoing study to assess the long-term durability of virologic res to 6.6 years after treatment; 95% (61/64) remain serum HBeAg nega

INTRON A therapy resulted in normalization of serum ALT in a signific each of two controlled studies (see TABLE 4). In a third study without (12/24) of patients receiving INTRON A therapy.

Virologic response was associated with a reduction in serum ALT to n

Improvement in liver histology was evaluated in Studies 1 and 3 by c semiquantitative Knodell Histology Activity Index. [9] No statistically si to control patients in Study 1. Although statistically significant histolo 10

Pediatrics The safety and efficacy of INTRON A Interferon alfa-2b, rec randomized controlled trial of 149 patients ranging from 1 year to 17 yea therapy administered subcutaneously three times a week (TIW) for 1 wee up to 24 weeks. The maximum weekly dosage was 10 million IU TIW. S identical to those described in the adult patient population.

Patients treated with INTRON A therapy had a better response (loss of H (24% [17/72] vs 10% [8/77] p=0.05). Sixteen of the 17 responders treate

normal serum ALT 12 to 24 months after completion of treatment. Serum
therapy. None of the control patients who had an HBV DNA and HBeAg
serum ALT was similar in patients treated with INTRON A therapy (17%
DNA <100 pg/mL were more likely to respond to INTRON A therapy th
Patients who contracted hepatitis B through maternal vertical transmissio
vs 31%, respectively). There was no evidence that the effects on HBV DN

ALT
IN CHRONIC
Treatment Gro

Study Number	*INTRON A 5 million IU QD*		*1*
1	16/38	(42%)	
2	--	--	
3	--	--	1
All Studies	**16/38**	**(42%)**	

* Reduction in serum ALT to no

† INTRON A treatment group vs

‡ Untreated control patients eval subgroup subsequently received not applicable (NA).

(*back to top*)

INDICATIONS AND USAGE

Hairy Cell Leukemia INTRON A Interferon alfa-2b, recombinant for I cell leukemia.

Malignant Melanoma INTRON A Interferon alfa-2b, recombinant for older with malignant melanoma who are free of disease but at high risk f

Follicular Lymphoma INTRON A Interferon alfa-2b, recombinant for **Experience**) follicular Non-Hodgkin's Lymphoma in conjunction with a older. Efficacy of INTRON A therapy in patients with low-grade, low-tu

Condylomata Acuminata INTRON A Interferon alfa-2b, recombinant age or older with condylomata acuminata involving external surfaces of t

The use of this product in adolescents has not been studied.

AIDS-Related Kaposi's Sarcoma INTRON A Interferon alfa-2b, recom or older with AIDS-Related Kaposi's Sarcoma. The likelihood of respons who have limited lymphadenopathy and who have a relatively intact imm

Chronic Hepatitis C INTRON A Interferon alfa-2b, recombinant for In or older with compensated liver disease who have a history of blood or b demonstrated that INTRON A therapy can produce meaningful effects on and reduction in liver necrosis and degeneration.

A liver biopsy should be performed to establish the diagnosis of chronic other causes of chronic hepatitis, including autoimmune hepatitis, should that the patient has compensated liver disease. The following patient entr should be considered before INTRON A treatment of patients with chron

- No history of hepatic encephalopathy, variceal bleeding, ascites, or oth
- Bilirubin
- Albumin Stable and within normal limits
- Prothrombin Time <3 seconds prolonged
- WBC >/=3000/mm ^{3}
- Platelets >/=70,000/mm ^{3}

Serum creatinine should be normal or near normal.

Prior to initiation of INTRON A therapy, CBC and platelet counts should tests should be repeated at weeks 1 and 2 following initiation of INTRON approximately 3-month intervals to assess response to treatment (see **DO**

Patients with preexisting thyroid abnormalities may be treated if thyroid- medication. TSH levels must be within normal limits upon initiation of I **PRECAUTIONS -- Laboratory Tests**).

INTRON A in combination with REBETOL (ribavirin, USP) Capsules is disease previously untreated with alfa interferon therapy or who have rela package insert for additional information.

Chronic Hepatitis B INTRON A Interferon alfa-2b, recombinant for In older with compensated liver disease. Patients who have been serum HB HBeAg positive) with elevated serum ALT are candidates for treatment. remission of this disease (loss of serum HBeAg), and normalization of se some responding patients.

Prior to initiation of INTRON A therapy, it is recommended that a liver b liver damage. The physician should establish that the patient has compen disease were used in the clinical studies and should be considered before

- No history of hepatic encephalopathy, variceal bleeding, ascites, or oth
- Bilirubin Normal
- Albumin Stable and within normal limits
- Prothrombin Time *Adults* <3 seconds prolonged *Pediatrics*
- WBC >/=4000/mm ^{3}
- Platelets *Adults* >/=100,000/mm ^{3} *Pediatrics* >/=

Patients with causes of chronic hepatitis other than chronic hepatitis B or recombinant for Injection. CBC and platelet counts should be evaluated p potential toxicity. These tests should be repeated at treatment weeks 1, 2, should be evaluated at treatment weeks 1, 2, 4, 8, 12, and 16. HBeAg, HB posttherapy, since patients may become virologic responders during the 6 (15/38) of responding patients lost HBeAg 1 to 6 months following the e so 1- to 6-months post-treatment.

A transient increase in ALT >/=2 × baseline value (flare) can occur durin pediatrics, this flare generally occurred 8 to 12 weeks after initiation of th *pediatrics* 59%, 10/17) than in nonresponders (*adults* 27%, 13/48; *pedia* mg/dL (>/=2 times ULN) occurred infrequently (*adults* 2%, 2/86; *pediat* therapy should be continued unless signs and symptoms of liver failure a including ALT, prothrombin time, alkaline phosphatase, albumin, and bi

(*back to top*)

DOSAGE AND ADMINISTRATION

IMPORTANT: INTRON A Interferon alfa-2b , is packaged as 1) po prefilled, multidose cartridges in a multidose pen device for subcutaneou is important that you carefully read the instructions below for the indicati

INTRON A SOLUTION FOR INJECTION IS NOT RECOMMEND

Hairy Cell Leukemia The recommended dosage of INTRON A Interfe million IU/m ^{2} administered intramuscularly (see **WARNINGS**) or subc continued treatment. **NOTE: The 50 million IU strength of the INTRO leukemia.** Higher doses are not recommended.

If severe adverse reactions develop, the dosage should be modified (50% abate. If persistent or recurrent intolerance develops following adequate d discontinued. The minimum effective INTRON A dose has not been esta

Malignant Melanoma The recommended INTRON A treatment regim intravenous (IV) infusion at a dose of 20 million IU/m ^{2} , followed by ma injection, at a dose of 10 million IU/m ^{2} .

In the clinical trial, the median daily INTRON A doses administered to p during the maintenance phase. **NOTE: INTRON A Solution for Injecti for the induction phase of malignant melanoma.**

Regular laboratory testing should be performed to monitor laboratory abn **Laboratory Tests**). If adverse reactions develop during INTRON A trea × upper limit of normal, treatment should be temporarily discontinued un the previous dose. If intolerance persists after dose adjustments or if gran INTRON A therapy should be discontinued.

Follicular Lymphoma The recommended dosage of INTRON A Interf week for up to 18 months in conjunction with an anthracycline-containin

In published reports, the doses of myelosuppressive drugs were reduced b by 33% (eg, from 21 to 28 days) when an alfa interferon was added to the toxicity. The following dose modification guidelines for hematologic tox the neutrophil count was <1500/mm ^{3} or the platelet count was <75,000/ neutrophil count <1000/mm ^{3} , or a platelet count <50,000/mm ^{3} , or redu

Reinstitution of the initial INTRON A dose (5 million IU TIW) was toler

INTRON A therapy should be discontinued if SGOT exceeds >5 × the up

Condylomata Acuminata The 10 million IU vial of INTRON A Powd alfa-2b, recombinant for Injection (bacteriostatic water for injection). Do than 1 mL of diluent since the injection would be subpotent. Do not use t Powder for Injection for the treatment of condylomata acuminata since th concentration. Do not use the 3 million IU vial or the 18 million IU mult condylomata acuminata since the concentrations are inappropriate for suc

Inject 1.0 million IU of INTRON A Interferon alfa-2b, recombinant for I Injection or 0.1 mL of the 5 million IU, 10 million IU, or 25 million IU s million IU/mL) into each lesion three times per week on alternate days, f similar syringe and a 25-to 30-gauge needle. The needle should be direct the skin (approximating that in the commonly used PPD test). This will d causing a small wheal. Care should be taken not to go beneath the lesion base of the lesion. Do not inject too superficially since this will result in many as five lesions can be treated at one time. To reduce side effects, IN Additionally, acetaminophen may be administered at the time of injection

The maximum response usually occurs 4 to 8 weeks after initiation of the has concluded are not satisfactory, a second course of treatment using the or changes in laboratory parameters (liver function tests, WBC, and plate

Patients with 6 to 10 condylomata may receive a second (sequential) cou condylomata per course of treatment. Patients with greater than 10 condy condylomata are present.

AIDS-Related Kaposi's Sarcoma The recommended INTRON A dosa intramuscularly. **NOTE: INTRON A Solution for Injection should NO inappropriate.** The 18 million and 25 million IU multidose strengths of AIDS-Related Kaposi's Sarcoma since the concentrations are inappropria

The selected dosage regimen should be maintained unless the disease pro develop, the dosage should be modified (50% reduction) or therapy shou initiate therapy at 30 million IU/m ^{2} TIW, the average dose tolerated at th end of 24 weeks of therapy.

When disease stabilization or a response to treatment occurs, treatment s

required by evidence of a severe opportunistic infection or adverse effect

Chronic Hepatitis C The recommended dosage of INTRON A Interfer million IU three times a week (TIW) administered subcutaneously or intr **should NOT be used for chronic hepatitis C.** In patients tolerating ther be extended to 18 to 24 months (72 to 96 weeks) at 3 million IU TIW to Chronic Hepatitis C). Patients who do not normalize their ALTs after 1 Consideration should be given to discontinuing these patients from thera

If severe adverse reactions develop during INTRON A treatment, the dos below. If intolerance persists after dose adjustment, INTRON A therapy

See REBETRON Combination Therapy package insert for dosing when u

Chronic Hepatitis B ***Adults*** The recommended dosage of INTRON A is 30 to 35 million IU per week, administered subcutaneously or intramu (TIW) for 16 weeks.

Pediatrics The recommended dosage of INTRON A Interferon alfa-2b, three times a week (TIW) for the first week of therapy followed by dose subcutaneously for a total therapy duration of 16 to 24 weeks. **NOTE: T Solution for Injection should NOT be used for chronic hepatitis B.**

If severe adverse reactions or laboratory abnormalities develop during IN appropriate, until the adverse reactions abate. If intolerance persists after

For patients with decreases in white blood cell, granulocyte, or platelet co

INTRON A Dose	*White Cell C*
Reduce 50%	<1.5 ×
Permanently Discontinue	<1.0 ×

INTRON A therapy was resumed at up to 100% of the initial dose when values.

At the discretion of the physician, the patient may self-administer the me

Preparation and Admi
alfa-2b, recom
for Intramuscular,
A

Reconstitution of INTRON A Powder for Injection Inject the amount of water for injection) stated in the chart below (diluent is supplied in either gently to hasten complete dissolution of the powder. The appropriate INT subcutaneously, or intralesionally (see **PATIENT INFORMATION SH**

A injection, it is essential to follow the procedure for proper disposal of s instructions).

INTRON A Powder for Injection is not indicated for use in infants and sh with the provided diluent it contains benzyl alcohol (see **WARNINGS**,

Preparation and Administration of INTRON A Interferon alfa-2b, recom

The infusion solution should be prepared immediately prior to use. Based alfa-2b, recombinant Powder for Injection should be reconstituted with th injected into a 100-mL bag of 0.9% Sodium Chloride Injection, USP. Th should be not less than 10 million IU/100 mL. The prepared solution sho

INTRON A Interferon alfa		
	3 million IU	5
Chronic Hepatitis B		
Chronic Hepatitis C	1 mL	
Hairy Cell Leukemia	1 mL	
AIDS-Related Kaposi's Sarcoma		
Condylomata Acuminata		
Malignant Melanoma induction phase ‡	1 mL *	
maintenance phase	1 mL *	
Follicular Lymphoma	1 mL	
* Use only for dose reduction.		
** IMPORTANT: For patients with co IU vial with only 1 mL of the diluent p million IU/mL to be administered intr		
† Based on the desired dose, the app administered intravenously.		
‡ This vial strength should be used o AIDS-Related Kaposi's Sarcoma or m inappropriate for all other indications.		

Please refer to the **Patient Information Sheet** for detailed, step-by-step i A, it is essential to follow the procedure for proper disposal of syringes a

Parenteral drug products should be inspected visually for particulate matt INTRON A Interferon alfa-2b, recombinant for Injection may be adminis

Stability INTRON A Interferon alfa-2b, recombinant Powder for Injecti

(113°F) for up to 7 days. After reconstitution with Diluent for INTRON A solution is stable for 1 month at 2° to 8°C (36° to 46°F). The reconstitute

Preparation and Administration of INTRON A Interferon alfa-2b, recom

INTRON A Solution for Injection is supplied in single-use vials, multido reconstitution prior to administration; the solution is clear and colorless.

Solution for Injection in Vials

For INTRON A Solution for Injection vials, the appropriate dose should intralesionally (5 million IU and 10 million IU single-use vials, and 25 m supplied with B-D Safey-Lok* syringes. The Safety-Lok* syringe contain an audible click when the green stripe on the safety sleeve covers the red

INTRON A Interferon alfa

	3 million IU	5 m I
Chronic Hepatitis B		
Chronic Hepatitis C	V	
Hairy Cell Leukemia	V	
Condylomata Acuminata		
Malignant Melanoma	V‡	
Follicular Lymphoma		

*This is a multidose vial which cont alfa-2b, recombinant per 3.8 mL in o each containing 3 million IU of INT Injection (for a label strength of 18 m

† This is a multidose vial which con alfa-2b, recombinant per 3.2 mL in o doses, each containing 5 million IU for Injection (for a label strength of

‡ Use only for dose reduction.

§ Use only for the 5 MIU daily regim

¶ Use only for maintenance treatmen

Solution for Injection in Multidose Pens

The INTRON A Solution for Injection multidose pen contains a prefilled individual doses using a simple dial mechanism. The needles provided in

pen only. A new needle is to be used each time a dose is delivered using Injection multidose pen is for single patient use only.

INTRON A Interfero in M	
	3 million mL *
Chronic Hepatitis B	
Chronic Hepatitis C	V
Hairy Cell Leukemia	V
Malignant Melanoma	
Follicular Lymphoma	
*The 3 million IU multidose pe interferon alfa-2b, recombinant p 0.2-mL doses each containing 3 Solution for Injection (for a labe	
**The 5 million IU multidose p interferon alfa-2b, recombinant p 0.2-mL doses each containing 5 Solution for Injection (for a labe	
***The 10 million IU multidose interferon alfa-2b, recombinant p 0.2-mL doses each containing 10 recombinant Solution for Injecti	

Please refer to the **Patient Information Sheet** for detailed, step-by-step i A, it is essential to follow the procedure for proper disposal of syringes a

Parenteral drug products should be inspected visually for particulate matt INTRON A Interferon alfa-2b, recombinant for Injection may be adminis

Stability INTRON A Interferon alfa-2b, recombinant Solution for Inject stable at 30°C (86°F) for up to 2 days. INTRON A Interferon alfa-2b, rec vial, is stable at 35°C (95°F) for up to 7 days and at 30°C (86°F) for up to

(*back to top*)

CONTRAINDICATIONS

INTRON A Interferon alfa-2b, recombinant for Injection is contraindicat the injection. REBETRON Combination Therapy containing INTRON A pregnant or by men whose female partners are pregnant. Extreme care m taking combination INTRON A/REBETOL therapy. Patients with autoim therapy. See REBETRON Combination Therapy package insert for addit

(*back to top*)

WARNINGS

General Moderate to severe adverse experiences may require modificat therapy. Because of the fever and other "flu-like" symptoms associated w debilitating medical conditions, such as those with a history of pulmonar ketoacidosis. Caution should also be observed in patients with coagulatio

Patients with platelet counts of less than 50,000/mm ^{3} should not be adm but instead by subcutaneous administration.

INTRON A therapy should be used cautiously in patients with a history o and/or previous or current arrhythmic disorder who require INTRON A t experiences, which include hypotension, arrhythmia, or tachycardia of 15 have been observed in some INTRON A treated patients. Some patients w cardiomyopathy was reported in approximately 2% of the AIDS-Related for Injection. Hypotension may occur during INTRON A administration, replacement to maintain intravascular volume.

Supraventricular arrhythmias occurred rarely and appeared to be correlat adverse experiences were controlled by modifying the dose or discontinu

DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH A preexisting psychiatric condition, especially depression, or a history of se recombinant for Injection. [11] INTRON A therapy should be discontinued treatment. Obtundation and coma have also been observed in some patien reversible upon discontinuation of therapy, full resolution of symptoms h may be used concurrently with caution and patients should be closely mo

Bone marrow toxicity. INTRON A therapy suppresses bone marrow fu anemia. It is advised that complete blood counts (CBC) be obtained pretr **Tests**). INTRON A therapy should be discontinued in patients who deve (see **DOSAGE AND ADMINISTRATION** : Guidelines for Dose Modi

Infrequently, patients receiving INTRON A therapy developed thyroid ab A Interferon alfa-2b, recombinant for Injection may alter thyroid status is cannot be maintained in the normal range by medication should not be tr of INTRON A therapy, serum TSH should be evaluated. Patients develop INTRON A therapy should have their thyroid function evaluated and app thyroid abnormalities during treatment whose thyroid function cannot be reversed thyroid dysfunction occurring during treatment.

Hepatotoxicity, including fatality, has been observed in interferon alfa tre recombinant for Injection. Any patient developing liver function abnorm should be discontinued.

Pulmonary infiltrates, pneumonitis and pneumonia, including fatality, ha INTRON A Interferon alfa-2b, recombinant for Injection. The etiologic e

developing fever, cough, dyspnea, or other respiratory symptoms should evidence of pulmonary function impairment, the patient should be closel While this has been reported more often in patients with chronic hepatitis diseases treated with interferon alfa.

Retinal hemorrhages, cotton-wool spots, and retinal artery or vein obstru those treated with INTRON A Interferon alfa-2b, recombinant for Injecti events appear to occur after use of the drug for several months, but also h have been present in some patients. Any patient complaining of changes treatment with INTRON A Interferon alfa-2b, recombinant for Injection, differentiated from those seen with diabetic or hypertensive retinopathy, patients with diabetes mellitus or hypertension.

Rare cases of autoimmune diseases including thrombocytopenia, vasculit rhabdomyolysis have been observed in patients treated with alfa interfero Injection. In very rare cases the event resulted in fatality. The mechanism clear. Any patient developing an autoimmune disorder during treatment s

Diabetes mellitus and hyperglycemia have been observed rarely in patien Symptomatic patients should have their blood glucose measured and foll antidiabetic regimen.

The 50 million IU strength of the INTRON A Powder for Injection is follicular lymphoma, chronic hepatitis C, or chronic hepatitis B. The Powder for Injection are not to be used for the intralesional treatmen would result in a hypertonic solution.

The INTRON A multidose pens, the 3 million IU vial, and the 18 mil the treatment of condylomata acuminata. The INTRON A multidose Solution for Injection are not to be used for the treatment of AIDS-R recommended for the intravenous treatment of malignant melanoma

The powder formulations of this product contain albumin, a derivative of processes, it carries an extremely remote risk for transmission of viral dis considered extremely remote. No cases of transmission of viral diseases

AIDS-Related Kaposi's Sarcoma INTRON A therapy should not be u **PHARMACOLOGY**). Also of note, there may be synergistic adverse e zidovudine. Patients receiving concomitant zidovudine have had a higher monitoring of the WBC count is indicated in all patients who are myelos effects of INTRON A Interferon alfa-2b, recombinant for Injection when unknown.

Chronic Hepatitis C and Chronic Hepatitis B Patients with decompe patients who are immunosuppressed transplant recipients should not be t reports of worsening liver disease, including jaundice, hepatic encephalo Therapy should be discontinued for any patient developing signs and sym

Chronic hepatitis B patients with evidence of decreasing hepatic syntheti who nevertheless meet the entry criteria to start therapy, may be at increa

INTRON A treatment. In such patients, if increases in ALT occur during including close monitoring of clinical symptomatology and liver function bilirubin. In considering these patients for INTRON A therapy, the poten

INTRON A Interferon alfa-2b, recombinant Powder for Injection when r recombinant for Injection (bacteriostatic water for injection) contains ben excessive exposure to benzyl alcohol. The amount of benzyl alcohol at w **Powder for Injection** is not indicated for use in infants and should not b

REBETRON Combination Therapy containing INTRON A and REBETO <10 g/dL was observed in approximately 10% of patients in clinical trial REBETRON Combination Therapy containing INTRON A and REBETO with caution in patients with moderate renal impairment. See REBETRO

(*back to top*)

PRECAUTIONS

General Acute serious hypersensitivity reactions (eg, urticaria, angioed treated patients; if such an acute reaction develops, the drug should be di have occurred in some patients following injection, but have not necessit

While fever may be related to the flu-like syndrome reported commonly

There have been reports of interferon, including INTRON A Interferon a therefore, INTRON A therapy should be used in these patients only if the

Variations in dosage, routes of administration, and adverse reactions exis interferon in any single treatment regimen.

Triglycerides Elevated triglyceride levels have been observed in patien should be managed as clinically appropriate. Severe hypertriglyceridemia A therapy should be considered for patients with persistently elevated tri pancreatitis, such as abdominal pain, nausea, or vomiting.

(*back to top*)

Drug Interactions Interactions between INTRON A Interferon alfa-2b, should be exercised when administering INTRON A therapy in combinat use of alfa interferon and theophylline decreases theophylline clearance,

Information for Patients Patients receiving INTRON A treatment shou treatment, and referred to the **PATIENT INFORMATION SHEET** . Th not a disclosure of all possible adverse or intended effects.

If home use is prescribed, a puncture-resistant container for the disposal thoroughly instructed in the importance of proper disposal and cautioned according to the directions provided by the physician (see **PATIENT IN**

Patients should be cautioned not to change brands of interferon without m

Patients receiving high INTRON A doses should be cautioned against pe machinery or driving a motor vehicle.

The most common adverse experiences occurring with INTRON A thera vomiting (see **ADVERSE REACTIONS**) and appear to decrease in sev by bedtime administration. Antipyretics may be used to prevent or partia of the hair.

It is advised that patients be well hydrated, especially during the initial st

INTRON A in combination with REBETOL (ribavirin, USP) Capsules th partners are pregnant. Extreme care must be taken to avoid pregnancy in therapy. Combination INTRON A/REBETOL therapy should not be initi initiation of therapy. See REBETRON Combination Therapy package ins

Laboratory Tests In addition to those tests normally required for moni INTRON A therapy, prior to beginning treatment and then periodically th

- Standard hematologic tests -- including hemoglobin, complete and d
- Blood chemistries -- electrolytes, liver function tests, and TSH.

Those patients who have preexisting cardiac abnormalities and/or are in a the course of treatment.

Mild-to-moderate leukopenia and elevated serum liver enzyme (SGOT) l alfa-2b, recombinant for Injection (see **ADVERSE REACTIONS**); ther

Baseline chest x-rays are suggested and should be repeated if clinically in

For malignant melanoma patients, differential WBC count and liver func monthly during the maintenance phase of therapy.

For specific recommendations in chronic hepatitis C and chronic hepatiti

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with IN determine carcinogenicity.

Interferon may impair fertility. In studies of interferon administration in n serum estradiol and progesterone concentrations have been reported in w not receive INTRON A therapy unless they are using effective contracep fertile men.

Mutagenicity studies have demonstrated that INTRON A Interferon alfa-

Studies in mice (0.1, 1.0 million IU/day), rats (4, 20, 100 million IU/kg/d IU/kg/day) injected with INTRON A Interferon alfa-2b, recombinant for evidence of toxicity. However, in cynomolgus monkeys (4, 20, 100 milli recombinant for Injection toxicity was observed at the mid and high dose

However, due to the known species-specificity of interferon, the effects i

INTRON A in combination with REBETOL (ribavirin, USP) Capsules sh package insert for additional information.

Pregnancy Category C INTRON A Interferon alfa-2b, recombinant fo monkeys) at 15 and 30 million IU/kg (estimated human equivalent of 5 a are no adequate and well-controlled studies in pregnant women. INTRON potential risk to the fetus.

Pregnancy Category X applies to the REBETRON Combination Therap **CONTRAINDICATIONS**). See REBETRON Combination Therapy pa

Nursing Mothers It is not known whether this drug is excreted in huma into the milk. Because of the potential for serious adverse reactions from nursing or to discontinue INTRON A therapy, taking into account the im

Pediatric Use *General* Safety and effectiveness in pediatric patients b hepatitis B.

Chronic Hepatitis B Safety and effectiveness in pediatric patients rangin trial (see **CLINICAL PHARMACOLOGY** , **INDICATIONS AND US** effectiveness in pediatric patients below the age of 1 year have not been e

INTRON A Interferon alfa-2b, recombinant **Powder for Injection** when recombinant for Injection (bacteriostatic water for injection) contains ben death in infants associated with excessive exposure to benzyl alcohol. Th is not known (see **WARNINGS Chronic Hepatitis B**).

(*back to top*)

ADVERSE REACTIONS

General The adverse experiences listed below were reported to be poss adverse reactions were mild to moderate in severity and were manageabl

The most frequently reported adverse reactions were "flu-like" symptoms observed generally at higher doses and may be difficult for patients to tol during the marketing surveillance of INTRON A Interferon alfa-2b, reco hallucinations, renal failure, and renal insufficiency. Very rarely, INTRO associated with aplastic anemia. Very rarely sarcoidosis or exacerbation o

	TREATMENT-RELATED AD *Do* *Percenta*			
	MALIGNANT MELANOMA	**FOLLICULAR LYMPHOMA**	**HAIRY CELL LEUKEMIA**	**C**
	20 MIU/m 2 - Induction (IV)			

	10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*
ADVERSE EXPERIENCE	N=143	N=135	N=145
Application-Site Disorders			20
injection site inflammation	--	1	--
other (	burning, injection site bleeding, injection site pain		
Blood Disorders (<5%)	anemia, anemia hypochromic, granulocytopenia, hepatitis C, 14% in chronic hepatitis B pediatrics) melanoma), thrombocytopenic purpura		
Body as a Whole			
facial edema	--	1	--
weight decrease	3	13	<1
other (	allergic reaction, cachexia, dehydration, earache, nonspecific, lymphadenitis, lymphadenopathy, m follicular lymphoma), phlebitis superficial, scrota		
Cardiovascular System Disorders (<5%)	angina, arrhythmia, atrial fibrillation, bradycardia extrasystoles, heart valve disorder, hematoma, hy postural hypotension, pulmonary embolism, Rayn		
Endocrine System Disorders (<5%)	aggravation of diabetes mellitus, goiter, gynecom virilism		
Flu-like Symptoms			
fever	81	56	68
headache	62	21	39
chills	54	--	46
myalgia	75	16	39
fatigue	96	8	61
increased sweating	6	13	8
asthenia	--	63	7
rigors	2	7	--
arthralgia	6	8	8
dizziness	23	--	12
influenza-like symptoms	10	18	37
back pain	--	15	19
dry mouth	1	2	19
chest pain	2	8	<1

malaise	6	--	--
pain (unspecified)	15	9	18
other (<5%)	chest pain substernal, hyperthermia, rhinitis, rhino		
Gastrointestinal System Disorders			
diarrhea	35	19	18
anorexia	69	21	19
nausea	66	24	21
taste alteration	24	2	13
abdominal pain	2	20	<5
loose stools	--	1	--
vomiting	‡	32	6
constipation	1	14	<1
gingivitis	2 ‡	7 ‡	--
dyspepsia	--	2	--
other (<5%)	abdominal ascites, abdominal distension, colitis, gastroenteritis, gastrointestinal disorder (7% in fo discoloration, gingival bleeding, gum hyperplasia melena, mouth ulceration, mucositis, oral hemorr stomatitis ulcerative, taste loss, tongue disorder, t		
Liver and Biliary System Disorders (<5%)	abnormal hepatic function tests, biliary pain, bilir (SGOT/SGPT) (elevated SGOT 63% in malignan pain (15% in chronic hepatitis C), and very rarely		
Musculoskeletal System Disorders			
musculoskeletal pain	--	18	--
other (<5%)	arteritis, arthritis, arthritis aggravated, arthrosis, b muscle atrophy, muscle weakness, polyarteritis no		
Nervous System and Psychiatric Disorders			
depression	40	9	6
paresthesia	13	13	6
impaired concentration	--	1	--
amnesia	§	1	<5
confusion	8	2	<5
hypoesthesia	--	1	<5
irritability	1	1	--
somnolence	1	2	<5
anxiety	1	9	5
insomnia	5	4	--
nervousness	1	1	--

decreased libido	1	1	<5
other (<5%)	abnormal coordination, abnormal dreaming, abno agitation (7% in chronic hepatitis B pediatrics) al convulsions, delirium, dysphonia, emotional labil hearing impairment, hot flashes, hyperesthesia, hy disorder, loss of consciousness, manic depression paroniria, parosmia, personality disorder, polyneu syncope, tinnitus, tremor, twitching, vertigo (8%		
Reproduction System Disorders (<5%)	amenorrhea (12% in follicular lymphoma), dysme pain, penis disorder, sexual dysfunction, uterine b		
Resistance Mechanism Disorders			
moniliasis	--	1	--
herpes simplex	1	2	--
other (<5%)	abscess, conjunctivitis, fungal infection, hemophi follicular lymphoma), infection parasitic, otitis m (7% in chronic hepatitis C)		
Respiratory System Disorders			
dyspnea	15	14	<1
coughing	6	13	<1
pharyngitis	2	8	<5
sinusitis	1	4	--
nonproductive coughing	2	7	--
nasal congestion	1	7	--
other (	asthma, bronchitis (10% in follicular lymphoma), hemoptysis, hypoventilation, laryngitis, lung fibro pneumothorax, rales, respiratory disorder, respira		
Skin and Appendages Disorders			
dermatitis	1	--	8
alopecia	29	23	8
pruritus	--	10	11
rash	19	13	25
dry skin	1	3	9
other (<5%)	abnormal hair texture, acne, cellulitis, cyanosis of necrolysis, erythema, erythema nodosum, follicul lipoma, maculopapular rash, melanosis, nail disor pruritus genital, psoriasis, psoriasis aggravated, p depigmentation, skin discoloration, skin nodule, u		
Urinary System Disorders (<5%)	albumin/protein in urine, cystitis, dysuria, hematu nocturia, polyuria (10% in follicular lymphoma),		

Vision Disorders (<5%)	abnormal vision, blurred vision, diplopia, dry eye
* Dash (--) indicates not reported	
† Vomiting was reported with nausea as a single term	
‡ Includes stomatitis/mucositis	
§ Amnesia was reported with confusion as a single term	
^ Percentages based upon a summary of all adverse events during 1	
¶ Predominantly lethargy	

Hairy Cell Leukemia The adverse reactions most frequently reported d symptoms of fever (68%), fatigue (61%), and chills (46%).

Malignant Melanoma The INTRON A dose was modified because of because of adverse events in 8% of the patients during induction and 18% was fatigue which was observed in 96% of patients. Other adverse reacti (92%), fever (81%), myalgia (75%), anorexia (69%), vomiting/nausea (6 diarrhea (35%), alopecia (29%), altered taste sensation (24%), dizziness/

Adverse reactions classified as severe or life threatening (ECOG Toxicity respectively. Severe adverse reactions recorded in >10% of INTRON A t myalgia (17%), headache (17%), chills (16%), and increased SGOT (14% INTRON A treated patients. No other grade 4 AE was reported in more t treated patients early in the clinical trial. No subsequent lethal hepatotoxi **PRECAUTIONS -- Laboratory Tests**).

Follicular Lymphoma Ninety-six percent of patients treated with CHV adverse event of any severity. Asthenia, fever, neutropenia, increased hep thrombocytopenia, paresthesia, and polyuria occurred more frequently in alone. Adverse reactions classified as severe or life threatening (World H patients included neutropenia (34%), asthenia (10%), and vomiting (10% in CHVP alone. One patient in each treatment group required hospitaliza

Twenty-eight percent of CHVP plus INTRON A treated patients had a te (10%) permanently stopped INTRON A therapy because of toxicity. The INTRON A arm and two patients in the CHVP arm had unwitnessed sud developed hepatotxicity leading to discontinuation of INTRON A. Other symptoms (2/135), and one patient each with exacerbation of ankylosing

Condylomata Acuminata Eighty-eight percent (311/352) of patients tr acuminata who were evaluable for safety, reported an adverse reaction du number of treated lesions increased from one to five. All 40 patients who

Adverse reactions and abnormal laboratory test values reported by patien during the initial INTRON A treatment period.

AIDS-Related Kaposi's Sarcoma In patients with AIDS-Related Kapo

treated with 30 million IU/m ^{2} three times a week and in 97% of the 29 p

Of these adverse reactions, those classified as severe (World Health Orga reactions in the 30 million IU/m ^{2} TIW study included: fatigue (20%), in confusion (3%), fever (3%), myalgia (3%), and nausea and vomiting (1% included: fever (24%), fatigue (17%), influenza-like symptoms (14%), dy GI hemorrhage, abnormal hepatic function, increased SGOT, myalgia, ca and coughing (1 patient each). Overall, the incidence of severe toxicity w

Chronic Hepatitis C Two studies of extended treatment (18 to 24 mon approximately 95% of all patients treated experience some type of advers events throughout treatment. Most adverse events reported are mild to m experienced a serious adverse event compared to 11/163 (7%) of those tr are similar in type and severity to those occurring during short-course the

Of the patients achieving a complete response after 6 months of therapy, therapy because of adverse events, and 23/79 (29%) experienced severe a

In patients using REBETRON Combination Therapy containing INTRON hemolytic anemia. Reductions in hemoglobin levels occurred within the occurred in approximately 10% of patients treated with INTRON A/REB information.

Chronic Hepatitis B ***Adults*** In patients with chronic hepatitis B, some QD and 90% of the 78 patients treated at 10 million IU TIW. Most of the reversible following the end of therapy.

Adverse reactions classified as severe (causing a significant interference The severe adverse reactions reported most frequently were the "flu-like" and other severe "flu-like" symptoms which occurred in 1% to 3% of pat (8%), anorexia (6%), depression (3%), nausea (3%), and vomiting (2%).

To manage side effects, the dose was reduced, or INTRON A therapy wa treatment due to adverse experiences.

Pediatrics In pediatric patients, the most frequently reported adverse ev (100%), gastrointestinal system disorders (46%), and nausea and vomitin the adverse events were life threatening. The majority were moderate to s

	ABNORMAL LABORATO
	Do
	Percen

	MALIGNANT MELANOMA	FOLLICULAR LYMPHOMA	HAIRY CELL LEUKEMIA	CON AC
	20 MIU/m² Induction (IV) 10 MIU/m² Maintenance (SC)	*5 MIU TIW/SC*	*2 MIU/m² TIW/SC*	
Laboratory Tests	N=143	N=135	N=145	
Hemoglobin	22	8	NA	
White Blood Cell Count	^	--	NA	
Platelet Count	15	13	NA	
Serum Creatinine	3	2	0	
Alkaline Phosphatase	13	--	4	
Lactate Dehydrogenase	1	--	0	
Serum Urea Nitrogen	12	4	0	
SGOT	63	24	4	
SGPT	2	--	13	
Granulocyte Count				
• Total	92	36	NA	
• 1000-<1500/mm³	66	--	--	
• 750-<1000/mm³	--	21	--	
• 500-<750/mm³	25	--	--	
• <500/mm³	1	13	--	

NA -- Not Applicable - Patients' initial hematologic laboratory test valu

* Decrease of >/=2 g/dL

** Decrease of >/=2 g/dL; 14% 2-<3 g/dL; 3% >/=3g/dL

† Decrease to <3000/mm³

‡ Decrease to <70,000/mm³

§ Neutrophils plus bands

^ White Blood Cell Count was reported as neutropenia

¶ Decrease of >/=2 g/dL; 20% 2-<3 g/dL; 6% >/=3 g/dL

(*back to top*)

OVERDOSAGE

Recommended doses of INTRON A therapy depends on indication. Dose MU/m ^{2} IV 5 days/week are tolerated in patient populations for certain in serious health effects. Toxic effects after ingestion of interferon alfa-2b a poison center is recommended.

Signs and Symptoms. The primary effects of an overdose are consistent REACTIONS).

Treatment. There is no specific antidote for interferon alfa-2b. Hemodia

(*back to top*)

HOW SUPPLIED

INTRON A Interferon alfa-2b, recombinant Powder for Injection I containing 6 INTRON A vials, 3 million IU per vial; 6 syringes of Diluen for injection) 1 mL per syringe for chronic hepatitis C; and 6 alcohol swa

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 5 milli Injection (bacteriostatic water for injection) 1 mL per vial; boxes contain

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 10 mil Injection (bacteriostatic water for injection) 2 mL per vial; boxes contain

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 18 mil Injection (bacteriostatic water for injection) 1 mL per vial; boxes contain

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 25 mil Injection (bacteriostatic water for injection) 5 mL per vial; boxes contain

INTRON A Interferon alfa-2b, recombinant Powder for Injection, 50 mil Injection (bacteriostatic water for injection) 1 mL per vial; boxes contain

Store INTRON A Interferon alfa-2b, recombinant Powder for Inject

INTRON A Interferon alfa-2b, recombinant Solution for Injection million IU (18 million IU) multidose pen (22.5 million IU per 1.5 mL pe alcohol swabs (NDC 0085-1242-01).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 6 dos pen); boxes containing 1 INTRON A multidose pen, six disposable need

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 6 dos boxes containing 1 INTRON A multidose pen, six disposable needles an

INTRON A Interferon alfa-2b, recombinant Solution for Injection INTRO * syringes with a safety sleeve; and 6 alcohol swabs (NDC 0085-1184-02

INTRON A Interferon alfa-2b, recombinant Solution for Injection INTRO * syringes with a safety sleeve; and 6 alcohol swabs (NDC 0085-1191-02

INTRON A Interferon alfa-2b, recombinant Solution for Injection INTRO Safety-Lok * syringes with a safety sleeve; and 6 alcohol swabs (NDC 00

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 18 mi of INTRON A Solution for Injection (NDC 0085-1168-01).

INTRON A Interferon alfa-2b, recombinant Solution for Injection, 25 mi INTRON A Solution for Injection (NDC 0085-1133-01).

Store INTRON A Interferon alfa-2b, recombinant Solution for Injec

(*back to top*)

REFERENCES

1. Smalley R, et al. *N Engl J Med.* 1992;327:1336-1341.
2. Aviles A, et al. *Leukemia and Lymphoma.* 1996;20:495-499.
3. Unterhalt M, et al. *Blood.* 1996;88 (10Suppl 1):1744A.
4. Schiller J, et al. *J Biol Response Mod.* 1989;8:252-261.
5. Poynard T, et al. *N Engl J Med.* 1995;332:(22)1457-1462.
6. Lin R, et al. *J Hepatol.* 1995;23:487-496.
7. Perrillo R, et al. *N Engl J Med.* 1990;323:295-301.
8. Perez V, et al. *J Hepatol.* 1990;11:S113-S117.
9. Knodell R, et al. *Hepatology.* 1981;1:431-435.
10. Perrillo R, et al. *Ann Intern Med.* 1991;115:113-115.
11. Renault P, et al. *Arch Intern Med.* 1987;147:1577-1580.
12. Kauppila A, et al. *Int J Cancer.* 1982;29:291-294.

(*back to top*)

Schering Corporation

Kenilworth, NJ 07033 USA

Rev. 8/01

*Safety-Lok is a registered trademark of Becton Dickinson and Company

Letter

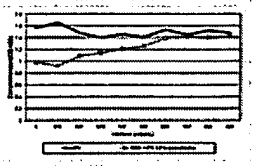
Efficacy of Interferon α-2b and Ribavirin Against *West Nile Virus* In Vitro

To the Editor: *West Nile virus* (WNV) infected humans in the Western Hemisphere for the first time in the late summer of 1999. During 1999 and 2000, nine deaths occurred among 80 patients with meningitis or encephalitis in New York City; Westchester County, New York; New Jersey; and Connecticut (1-3). Effective antiviral agents are unknown for infections caused by WNV. Odelola (4) described 83% survival of WNV-infected mice and eradication of virus from brain when 1.5 mg of ribavirin was administered by intraperitoneal injection after virus inoculation. Survival of controls was 25%. More recently, Jordan et al. have reported inhibition of WNV by a relatively high concentration of ribavirin (200 M) given after infection of human oligodendroglial cells in vitro (5). Shahar et al. (6) reported protection of fetal mouse spinal cord tissues with mouse alpha and beta interferon before inoculation with WNV. We tested human recombinant interferon alpha-2b and ribavirin for activity against WNV in a primate cell system similar to that used to measure the effect of these agents on *Bovine viral diarrhea virus*, a cultivatable, closely related surrogate for *Hepatitis C virus*.

Vero cells were cultured at 37° and 5% CO_2 in a 96-well microtiter plate. Approximately 13,000 cells were seeded in each well 24 hours before specific concentrations of ribavirin or interferon alpha-2b were added. Approximately 2.5 X 10^3 PFU of WNV isolated from *Culex pipiens* (7) was added 1.5-2 hours after or before the addition of interferon alpha-2b or ribavirin to Vero cells. Forty-four hours after treatment, a colorimetric proliferation assay was used to measure viable cells in each treated well according to the protocol of Promega (Madison, WI). Cells exposed to specific concentrations of antiviral compounds, but without WNV, were used as negative controls.

Interferon alpha-2b was protective and therapeutic. Interferon alpha-2b inhibited viral cytotoxicity at low dosage when applied before or after infection of cells with WNV. For example, viral protection was observed from 3,000 U/mL to 188 U/mL 2 hours before infection of cells with WNV. Interferon alpha-2b was also therapeutic when applied after cells were infected with WNV. Virus-induced cytotoxicity was inhibited by concentrations of ≥5.9 U/mL when added 1.5 hours after infection (Figure). The optical density 490 values in these tests were significantly different ($p<0.05$, using Tukey HSD multiple comparison test) when compared with the uninfected cells.

Figure



Click to view enlarged image

Figure. Effect of varying concentrations of interferon alpha-2b (FN) on *West Nile virus*-infected Vero cells. The vertical axis represents a colorimetric assay of cellular lactic dehydrogenase, which is directly proportional to cell viability and proliferation. OD = optical density.

Ribavirin was protective but not therapeutic in vitro. Cells were protected at dosages of 400 and 500 μM but not at dosages of 300 μM of ribavirin applied 2 hours before infection of cells with WNV. A cytotoxic effect of ribavirin occurred at concentrations of 600-1,000 μM.

In humans, daily doses of 3 million units of interferon result in serum levels of 10-20 U/mL, well above that required for in vitro efficacy (8). In contrast, oral ribavirin doses of 2,400 mg daily yield a steady-state serum concentration of 3-4 μg/mL after several days, approximately 12-40-fold less than the in vitro inhibitory concentrations of 200-500 M (50-125 μg/mL) noted by Jordan et al. (5) and in this study. Intravenous administration of 4 g daily, as used in the treatment of Lassa fever, would be required to reach a potentially effective serum concentration (9,10). However, intracellular accumulation and phosphorylation of ribavirin may account for its therapeutic effect in mice (4).

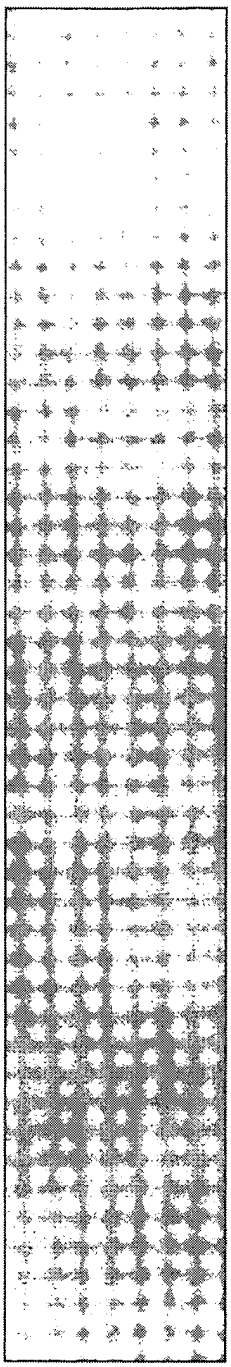
We conclude that interferon alpha-2b possesses greater therapeutic activity in vitro than ribavirin, with a potentially greater therapeutic ratio in humans. Whether combination therapy, as employed against hepatitis C, may be optimal requires further study.

Acknowledgments

Schering-Plough Research Institute provided technical quantities of interferon alpha-2b and ribavirin. Paul Glue, Paul Ingravallo, and Gerald Hajian provided helpful information. Jodi Correia, Bonnie Hamid, and Jeffrey Ward provided technical assistance. Noriel Mariano assisted in preparing the manuscript. Dr. Johnson Y.N. Lau collaborated in protocol development.

This study was supported in part by the BMA Medical Foundation, the Beatrice Snyder Foundation, the Hugaton Foundation, and the U.S. Department of Agriculture, Specific Cooperative Agreement 58-6615-1-20.

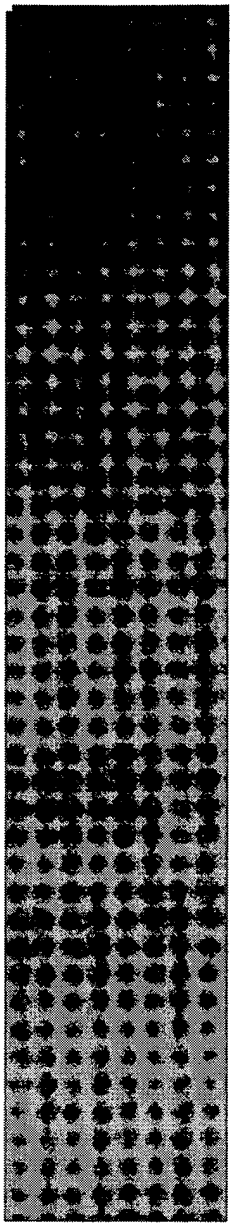
John F. Anderson* and James J. Rahal†
*Connecticut Agricultural Experiment Station, New Haven, Connecticut, USA; and †New York Hospital Queens and Weill College of Medicine, Cornell University,



New York, New York, USA

References

1. Centers for Disease Control and Prevention. Guidelines for surveillance, prevention, and control of West Nile Virus infection—United States. MMWR Morb Mortal Wkly Rep 2000;49:25-8
2. Layton M. West Nile virus final update for the 2000 season. Yew York: City of New York Department of Health Communicable Disease Program; 2000. p. 1-4.
3. Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, et al. Origin of the West Nile virus responsible for an outbreak of encephalitis in the Northeastern United States. Science 1999;286:2333-7.
4. Odelola HA. Antiviral activity of Virazole on replication of viruses isolated in Nigeria. In: Siegenthaler W, Luthy R, editors. Current chemotherapy (Proc 10th International Congress of Chemotherapy, Zurich). Vol. 1. Washington: American Society of Microbiology; 1978;1:3343-5.
5. Jordan I, Briese T, Fischer N, Lau JYN, Lipkin WI. Ribavirin inhibits West Nile virus replication and cytopathic effect in neural cells. J Infect Dis 2000;182:1214-17.
6. Shahar A, Lustig S, Akov Y, Schneider P, Levin R Different pathogenicity of encephalitic togaviruses in organotypic cultures of spinal cord slices. J Neurosci Res 1990;25:345-52.
7. Anderson JF, Andreadis TG, Vossbrinck CR, Tirrell S, Wakem EM, French RA, et al. Isolation of West Nile virus from mosquitoes, crows, and a Cooper's hawk in Connecticut. Science 1999;286:2331-3.
8. Khakoo S, Glue P, Grellier H, Wells B, Bell A, Dash C, et al. Ribavirin and interferon alpha 2-b in chronic hepatitis C: assessment of possible pharmacokinetic and pharmacodynamic inter ction. Br J Clin Pharmacol 1998;46:563-70.
9. Laskin OL, Lougstreth JA, Hart CC, Scavuzzo, D, Kalman CM, Connor JD, et al. Ribavirin disposition in high risk patients for acquired immunodeficiency syndrome. Clin Pharmacol Therap 1987;41:546-55.
10. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever. Effective therapy with ribavirin. N Engl J Med 1986;314:20-6.



Comments to the EID Editors

Please use this form to submit comments to the EID Editors.

Comments:

Email (optional)

Submit Reset

Home | Top of Page | Current Issue | *Expedited* | Upcoming Issue | Past Issue | EID Search | Contact Us | Accessibility | Privacy Policy Notice | CDC Home | Search | Health Topics A-Z

This page last reviewed January 11, 2002

Emerging Infectious Diseases Journal
National Center for Infectious Diseases
Centers for Disease Control and Prevention

URL: http://www.cdc.gov/ncidod/eid/vol8no1/01-0252.htm

1: Expert Opin Pharmacother. 2001 Aug;2(8):1317-24. Related Articles, Links

Ribavirin--current status of a broad spectrum antiviral agent.

Snell NJ.

Host Defence Unit, National Heart and Lung Institute, London, UK.

Ribavirin is a very broad-spectrum virustatic antiviral agent, first synthesised in 1972. It is characterised by low toxicity apart from reversible anaemia, usually mild. Its multiple mechanisms of action mean that viral resistance rarely develops. It can be administered orally, intravenously, or via a nebuliser. It has shown varying degrees of clinical efficacy in a variety of human diseases including respiratory tract infections due to respiratory syncytial virus and influenza, measles, herpesvirus infections, HIV infection, Lassa fever, haemorrhagic fever with renal syndrome, and (in combination with IFN-alpha) chronic hepatitis C infection. It may well prove of value against other emerging exotic infections (e.g., West Nile virus, Nipah virus).

Publication Types:
- Review
- Review Literature

PMID: 11585000 [PubMed - indexed for MEDLINE]

Stedman's Dictionary
Define:
Search

Document Outline
- Warnings
- Description
- Chemical Structure
- Clinical Pharmacology
- Indications and Usage
- Contraindications
- Warnings (2)
- Precautions
- Adverse Reactions
- Overdosage
- Dosage and Administration
- How Supplied
- Product Photo

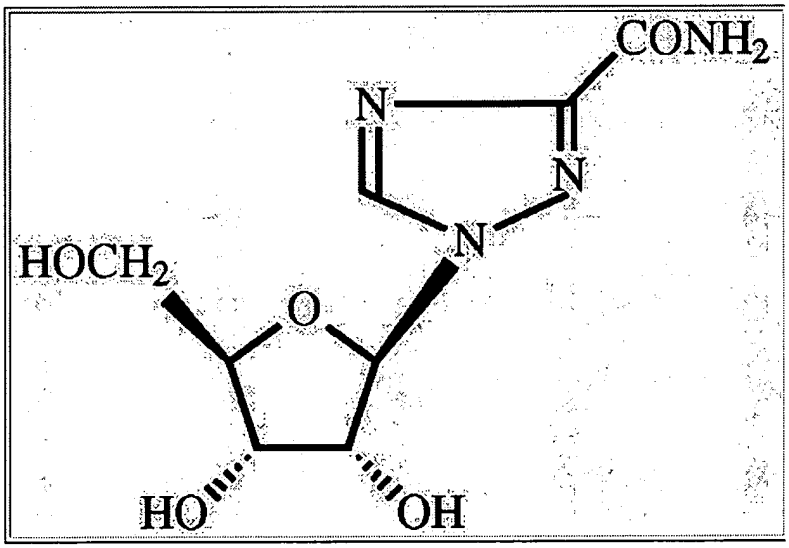
PDR® entry for

COPEGUS™ (Roche Laboratories)
(ribavirin, USP)
TABLETS

(*back to top*)

DESCRIPTION

COPEGUS, the Hoffmann-La Roche brand name for ribavirin, is a nucl analogue with antiviral activity. The chemical name of ribavirin is 1-(beta)-D-ribofuranosyl-1 *H* -1,2,4-triazole-3-carboxamide and has following structural formula:



The empirical formula of ribavirin is $C_8H_{12}N_4O_5$ and the molecula 244.2. Ribavirin is a white to off-white powder. It is freely soluble in slightly soluble in anhydrous alcohol.

COPEGUS (ribavirin) is available as a light pink to pink colored, flat, oval-shaped, film-coated tablet for oral administration. Each tablet co 200 mg of ribavirin and the following inactive ingredients: pregelatini starch, microcrystalline cellulose, sodium starch glycolate, corn starch magnesium stearate. The coating of the tablet contains Chromatone-Opadry® Pink (made by using hydroxypropyl methyl cellulose, talc, t dioxide, synthetic yellow iron oxide, and synthetic red iron oxide), eth cellulose (ECD-30), and triacetin.

Mechanism of Action

Ribavirin is a synthetic nucleoside analogue. The mechanism by whic

combination of ribavirin and an interferon product exerts its effects a hepatitis C virus has not been fully established.

(*back to top*)

CLINICAL PHARMACOLOGY

Pharmacokinetics

Multiple dose ribavirin pharmacokinetic data are available for HCV pa received ribavirin in combination with peginterferon alfa-2a. Followin administration of 1200 mg/day with food for 12 weeks mean±SD (n= weight >75 kg) AUC $_{0\text{-}12hr}$ was 25,361±7110 ng·hr/mL and C $_{max}$ wa 2748±818 ng/mL. The average time to reach C $_{max}$ was 2 hours. Trou ribavirin plasma concentrations following 12 weeks of dosing with foo 1662±545 ng/mL in HCV infected patients who received 800 mg/day and 2112±810 ng/mL in patients who received 1200 mg/day (n=75; weight >75 kg).

The terminal half-life of ribavirin following administration of a single o of COPEGUS is about 120 to 170 hours. The total apparent clearance administration of a single oral dose of COPEGUS is about 26 L/h. The extensive accumulation of ribavirin after multiple dosing (twice daily) the C $_{max}$ at steady state was four-fold higher than that of a single do

Effect of Food on Absorption of Ribavirin

Bioavailability of a single oral dose of ribavirin was increased by co-administration with a high-fat meal. The absorption was slowed (T doubled) and the AUC $_{0\text{-}192h}$ and C $_{max}$ increased by 42% and 66%, respectively, when COPEGUS was taken with a high-fat meal compare fasting conditions (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Elimination and Metabolism

The contribution of renal and hepatic pathways to ribavirin eliminatio administration of COPEGUS is not known. In vitro studies indicate tha is not a substrate of CYP450 enzymes.

Special Populations

Race

There were insufficient numbers of non-Caucasian subjects studied to adequately determine potential pharmacokinetic differences between populations.

Renal Dysfunction

The pharmacokinetics of ribavirin following administration of COPEGU not been studied in patients with renal impairment and there are limi from clinical trials on administration of COPEGUS in patients with crea clearance <50 mL/min. Therefore, patients with creatinine clearance

mL/min should not be treated with COPEGUS (see **WARNINGS** and **D AND ADMINISTRATION**).

Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of ribavirin administration of COPEGUS has not been evaluated. The clinical trials COPEGUS were restricted to patients with Child-Pugh class A disease.

Pediatric Patients

Pharmacokinetic evaluations in pediatric patients have not been perfo

Elderly Patients

Pharmacokinetic evaluations in elderly patients have not been perform

Gender

Ribavirin pharmacokinetics, when corrected for weight, are similar in female patients.

Drug Interactions

In vitro studies indicate that ribavirin does not inhibit CYP450 enzym

Nucleoside Analogues

Ribavirin has been shown in vitro to inhibit phosphorylation of zidovu stavudine which could lead to decreased antiretroviral activity. Expos didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate increased when didanosine is co-administered with ribavirin, which co or worsen clinical toxicities (see **PRECAUTIONS** : **Drug Interaction**

Clinical Studies

The safety and effectiveness of PEGASYS in combination with COPEGU treatment of hepatitis C virus infection were assessed in two randomi controlled clinical trials. All patients were adults, had compensated liv disease, detectable hepatitis C virus, liver biopsy diagnosis of chronic and were previously untreated with interferon. Approximately 20% of in both studies had compensated cirrhosis (Child-Pugh class A).

In study NV15801 (described as study 4 in the PEGASYS Package Ins patients were randomized to receive either PEGASYS 180 µg sc once (qw) with an oral placebo, PEGASYS 180 µg qw with COPEGUS 1000 (body weight <75 kg) or 1200 mg po (body weight >/=75 kg) or REB (interferon alfa-2b 3 MIU sc tiw plus ribavirin 1000 mg or 1200 mg p patients received 48 weeks of therapy followed by 24 weeks of treatm follow-up. COPEGUS or placebo treatment assignment was blinded. P combination with COPEGUS resulted in a higher SVR (defined as unde HCV RNA at the end of the 24-week treatment-free follow-up period) to PEGASYS alone or interferon alfa-2b and ribavirin (Table 1). In all arms, patients with viral genotype 1 regardless of viral load, had a lo response rate to PEGASYS in combination with COPEGUS compared to with other viral genotypes.

Table 1 Sustained Virologic Response (SVR) to Combination Th (Study NV15801 *)			
	Interferon alfa-2b+ Ribavirin 1000 mg or 1200 mg	**PEGASYS + placebo**	**PEGASY COPEG 1000 mg or 1**
All patients	197/444 (44%)	65/224 (29%)	241/453 (
Genotype 1	103/285 (36%)	29/145 (20%)	132/298 (
Genotypes 2-6	94/159 (59%)	36/79 (46%)	109/155 (
Difference in overall treatment response (PEGASYS/ COPEGUS-Interferon alfa-2b/ribavirin) was 9% (95% CI 2.3, 15.3).			
* Described as study 4 in the PEGASYS Package Insert.			

In study NV15942 (described as study 5 in the PEGASYS Package Ins patients received PEGASYS 180 µg sc qw and were randomized to tre either 24 or 48 weeks and to a COPEGUS dose of either 800 mg or 10 mg/1200 mg (for body weight <75 kg/>/=75 kg). Assignment to the treatment arms was stratified by viral genotype and baseline HCV vir Patients with genotype 1 and high viral titer (defined as >2 × 10^6 HC copies/mL serum) were preferentially assigned to treatment for 48 w

Genotype 1

Irrespective of baseline viral titer, treatment for 48 weeks with PEGAS 1000 mg or 1200 mg of COPEGUS resulted in higher SVR (defined as undetectable HCV RNA at the end of the 24-week treatment-free follo period) compared to shorter treatment (24 weeks) and/or 800 mg CO

Genotype non-1

Irrespective of baseline viral titer, treatment for 24 weeks with PEGAS 800 mg of COPEGUS resulted in a similar SVR compared to longer tre (48 weeks) and/or 1000 mg or 1200 mg of COPEGUS (see Table 2).

Table 2 Sustained Virologic Response as a Function of Genotyp (Study NV15942 *)				
	24 Weeks Treatment		**48 Weeks Treatme**	
	PEGASYS + COPEGUS 800 mg (N=207)	**PEGASYS + COPEGUS 1000 mg or 1200 mg ** (N=280)**	**PEGASYS + COPEGUS 800 mg (N=361)**	**PEGA COPE 1000 m 1200 m (N=**
Genotype 1	29/101 (29%)	48/118 (41%)	99/250 (40%)	138/271
Gentoype 2-3	79/96 (82%)	116/144 (81%)	75/99 (76%)	117/153
*Described as study 5 in the PEGASYS Package Insert.				
**1000 mg for body weight <75 kg; 1200 mg for body weight >/=75 k				

Among the 36 patients with genotype 4, response rates were similar observed in patients with genotype 1 (data not shown). The numbers patients with genotype 5 and 6 were too few to allow for meaningful assessment.

Treatment Response in Patient Subgroups

Treatment response rates are lower in patients with poor prognostic f receiving pegylated interferon alpha therapy. In studies NV15801 and NV15942, treatment response rates were lower in patients older than (50% vs 66%), in patients with cirrhosis (47% vs 59%), in patients w over 85 kg (49% vs 60%), and in patients with genotype 1 with high viral load (43% vs 56%). African American patients had lower respon compared to Caucasians.

Paired liver biopsies were performed on approximately 20% of patien studies NV15801 and NV15942. Modest reductions in inflammation co to baseline were seen in all treatment groups.

In studies NV15801 and NV15942, lack of early virologic response at (defined as HCV RNA undetectable or >2log $_{10}$ lower than baseline) w grounds for discontinuation of treatment. Of patients who lacked an e response at 12 weeks and completed a recommended course of thera a protocol-defined option to discontinue therapy, 5/39 (13%) achieve Of patients who lacked an early viral response at 24 weeks, nineteen a full course of therapy and none achieved an SVR.

(*back to top*)

INDICATIONS AND USAGE

COPEGUS in combination with PEGASYS (peginterferon alfa-2a) is ind the treatment of adults with chronic hepatitis C virus infection who ha compensated liver disease and have not been previously treated with alpha. Patients in whom efficacy was demonstrated included patients compensated liver disease and histological evidence of cirrhosis (Chil class A).

(*back to top*)

CONTRAINDICATIONS

COPEGUS (ribavirin) is contraindicated in:

- Patients with known hypersensitivity to COPEGUS or to any comp the tablet.
- Women who are pregnant.
- Men whose female partners are pregnant.
- Patients with hemoglobinopathies (eg, thalassemia major or sick anemia).

COPEGUS and PEGASYS combination therapy is contraindicated in pa with:

- Autoimmune hepatitis.

- Hepatic decompensation (Child-Pugh class B and C) before or du treatment.

(*back to top*)

WARNINGS

COPEGUS must not be used alone because ribavirin monothera effective for the treatment of chronic hepatitis C virus infection safety and efficacy of COPEGUS have only been established wh together with PEGASYS (pegylated interferon alfa-2a, recombi

COPEGUS and PEGASUS should be discontinued in patients who deve evidence of hepatic decompensation during treatment.

There are significant adverse events caused by COPEGUS/PEG therapy, including severe depression and suicidal ideation, hem anemia, suppression of bone marrow function, autoimmune an infectious disorders, pulmonary dysfunction, pancreatitis, and The PEGASYS package insert and MEDICATION GUIDE should b reviewed in their entirety prior to initiation of combination tre for additional safety information.

General

Treatment with COPEGUS and PEGASYS should be administered unde guidance of a qualified physician and may lead to moderate to severe experiences requiring dose reduction, temporary dose cessation or discontinuation of therapy.

Pregnancy

Ribavirin may cause birth defects and/or death of the exposed Extreme care must be taken to avoid pregnancy in female pati in female partners of male patients. Ribavirin has demonstrate significant teratogenic and/or embryocidal effects in all anima in which adequate studies have been conducted. These effects at doses as low as one twentieth of the recommended human d ribavirin. COPEGUS THERAPY SHOULD NOT BE STARTED UNLES REPORT OF A NEGATIVE PREGNANCY TEST HAS BEEN OBTAINE IMMEDIATELY PRIOR TO PLANNED INITIATION OF THERAPY. should be instructed to use at least two forms of effective contraception during treatment and for at least six months aft treatment has been stopped. Pregnancy testing should occur m during COPEGUS therapy and for six months after therapy has (see CONTRAINDICATIONS and PRECAUTIONS : Information f Patients and Pregnancy: Category X).

Anemia

The primary toxicity of ribavirin is hemolytic anemia (hemoglo g/dL), which was observed in approximately 13% of COPEGUS PEGASYS treated patients in clinical trials (see PRECAUTIONS Laboratory Tests). The anemia associated with COPEGUS occu 1 to 2 weeks of initiation of therapy. BECAUSE THE INITIAL DR HEMOGLOBIN MAY BE SIGNIFICANT, IT IS ADVISED THAT

HEMOGLOBIN OR HEMATOCRIT BE OBTAINED PRETREATMENT WEEK 2 AND WEEK 4 OF THERAPY OR MORE FREQUENTLY IF CLINICALLY INDICATED. Patients should then be followed as c appropriate.

Fatal and nonfatal myocardial infarctions have been reported i patients with anemia caused by ribavirin. Patients should be a for underlying cardiac disease before initiation of ribavirin the Patients with pre-existing cardiac disease should have electrocardiograms administered before treatment, and should appropriately monitored during therapy. If there is any deterio cardiovascular status, therapy should be suspended or discont (see DOSAGE AND ADMINISTRATION : COPEGUS Dose Modifica Guidelines). Because cardiac disease may be worsened by dru induced anemia, patients with a history of significant or unstab cardiac disease should not use COPEGUS (see ADVERSE REACT

Pulmonary

Pulmonary symptoms, including dyspnea, pulmonary infiltrates, pneu and occasional cases of fatal pneumonia, have been reported during t with ribavirin and interferon. In addition, sarcoidosis or the exacerbat sarcoidosis has been reported. If there is evidence of pulmonary infilt pulmonary function impairment, the patient should be closely monito appropriate, combination COPEGUS/PEGASYS treatment should be discontinued.

Other

COPEGUS and PEGASYS therapy should be suspended in patients with and symptoms of pancreatitis, and discontinued in patients with conf pancreatitis.

COPEGUS should not be used in patients with creatinine clearance <5 (see **CLINICAL PHARMACOLOGY** : **Special Populations**).

COPEGUS must be discontinued immediately and appropriate medica instituted if an acute hypersensitivity reaction (eg, urticaria, angioede bronchoconstriction, anaphylaxis) develops. Transient rashes do not n interruption of treatment.

(*back to top*)

PRECAUTIONS

The safety and efficacy of COPEGUS and PEGASYS therapy for the tre HIV infection, adenovirus, RSV, parainfluenza or influenza infections h been established. COPEGUS should not be used for these indications. for inhalation has a separate package insert, which should be consult ribavirin inhalation therapy is being considered.

The safety and efficacy of COPEGUS and PEGASYS therapy have not b established in liver or other organ transplant patients, patients with decompensated liver disease due to hepatitis C virus infection, patien non-responders to interferon therapy or patients co-infected with HBV

Information for Patients

Patients must be informed that ribavirin may cause birth defects and/ of the exposed fetus. COPEGUS therapy must not be used by women pregnant or by men whose female partners are pregnant. Extreme ca be taken to avoid pregnancy in female patients and in female partner patients taking COPEGUS therapy and for 6 months posttherapy. COP therapy should not be initiated until a report of a negative pregnancy been obtained immediately prior to initiation of therapy. Patients mus a pregnancy test monthly during therapy and for 6 months postthera

Female patients of childbearing potential and male patients with fema partners of childbearing potential must be advised of the teratogenic/embryocidal risks and must be instructed to practice effe contraception during COPEGUS therapy and for 6 months posttherapy should be advised to notify the physician immediately in the event of pregnancy (see **CONTRAINDICATIONS** and **WARNINGS**).

To monitor maternal-fetal outcomes of pregnant women exposed to C the COPEGUS Pregnancy Registry has been established. Physicians an are strongly encouraged to register by calling 1-800-526-6367.

The most common adverse event associated with ribavirin is anemia, may be severe (see **ADVERSE REACTIONS**). Patients should be adv laboratory evaluations are required prior to starting COPEGUS therap periodically thereafter (see **Laboratory Tests**). It is advised that pa well hydrated, especially during the initial stages of treatment.

Patients who develop dizziness, confusion, somnolence, and fatigue s cautioned to avoid driving or operating machinery.

Patients should be informed regarding the potential benefits and risks attendant to the use of COPEGUS. Instructions on appropriate use sh given, including review of the contents of the enclosed MEDICATION G which is not a disclosure of all or possible adverse effects.

Patients should be advised to take COPEGUS with food.

Laboratory Tests

Before beginning COPEGUS therapy, standard hematological and bioc laboratory tests must be conducted for all patients. Pregnancy screen women of childbearing potential must be done.

After initiation of therapy, hematological tests should be performed a and 4 weeks and biochemical tests should be performed at 4 weeks. testing should be performed periodically during therapy. Monthly preg testing should be done during combination therapy and for 6 months discontinuing therapy.

The entrance criteria used for the clinical studies of COPEGUS and PE combination therapy may be considered as a guideline to acceptable values for initiation of treatment:

- Platelet count >/=90,000 cells/mm ^{3}
- Absolute neutrophil count (ANC) >/=1500 cells/mm ^{3}

- TSH and T_4 within normal limits or adequately controlled thyroid
- ECG (see **WARNINGS**)

The maximum drop in hemoglobin usually occurred during the first 8 initiation of COPEGUS therapy. Because of this initial acute drop in he it is advised that a complete blood count should be obtained pretreat at week 2 and week 4 of therapy or more frequently if clinically indica Additional testing should be performed periodically during therapy. Pa should then be followed as clinically appropriate.

Drug Interactions

Results from a pharmacokinetic sub-study demonstrated no pharmac interaction between PEGASYS (peginterferon alfa-2a) and ribavirin.

Nucleoside Analogues

Didanosine

Co-administration of COPEGUS and didanosine is not recommended. fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, a symptomatic hyperlactatemia/lactic acidosis have been reported in cl (see **CLINICAL PHARMACOLOGY**: **Drug Interactions**).

Stavudine and Zidovudine

Ribavirin can antagonize the in vitro antiviral activity of stavudine an zidovudine against HIV. Therefore, concomitant use of ribavirin with e these drugs should be avoided (see **CLINICAL PHARMACOLOGY**: **D Interactions**).

Carcinogenesis, Mutagenesis, Impairment of Fertilit

Carcinogenesis

The carcinogenic potential of ribavirin has not been fully determined. (+/-) mouse carcinogenicity study at doses up to the maximum tolera of 100 mg/kg/day, ribavirin was not oncogenic. However, on a body s area basis, this dose was 0.5 times maximum recommended human 2 dose of ribavirin. A study to assess the carcinogenic potential of ribav is ongoing.

Mutagenesis

Ribavirin demonstrated mutagenic activity in the in vitro mouse lymp assay. No clastogenic activity was observed in an in vivo mouse micro assay at doses up to 2000 mg/kg. However, results from studies pub the literature show clastogenic activity in the in vivo mouse micronuc at oral doses up to 2000 mg/kg. A dominant lethal assay in rats was indicating that if mutations occurred in rats they were not transmitted male gametes. However, potential carcinogenic risk to humans canno excluded.

Impairment of Fertility

In a fertility study in rats, ribavirin showed a marginal reduction in sp counts at the dose of 100 mg/kg/day with no effect on fertility. Upon

of treatment, total recovery occurred after 1 spermatogenesis cycle. Abnormalities in sperm were observed in studies in mice designed to the time course and reversibility of ribavirin-induced testicular degen doses of 15 to 150 mg/kg/day (approximately 0.1-0.8 times the max recommended human 24-hour dose of ribavirin) administered for 3 to months. Upon cessation of treatment, essentially total recovery from ribavirin-induced testicular toxicity was apparent within 1 or 2 sperm cycles.

Female patients of childbearing potential and male patients with fema partners of childbearing potential should not receive COPEGUS unless patient and his/her partner are using effective contraception (two reli forms). Based on a multiple dose half-life ($t_{1/2}$) of ribavirin of 12 da effective contraception must be utilized for 6 months posttherapy (ie, half-lives of clearance for ribavirin).

No reproductive toxicology studies have been performed using PEGAS combination with COPEGUS. However, peginterferon alfa-2a and riba administered separately, each has adverse effects on reproduction. It assumed that the effects produced by either agent alone would also b by the combination of the two agents.

Pregnancy

Pregnancy: Category X (see CONTRAINDICATIONS)

Ribavirin produced significant embryocidal and/or teratogenic effects animal species in which adequate studies have been conducted. Malfo of the skull, palate, eye, jaw, limbs, skeleton, and gastrointestinal tra noted. The incidence and severity of teratogenic effects increased wit escalation of the drug dose. Survival of fetuses and offspring was red

In conventional embryotoxicity/teratogenicity studies in rats and rabb observed no-effect dose levels were well below those for proposed cli (0.3 mg/kg/day for both the rat and rabbit; approximately 0.06 times recommended human 24-hour dose of ribavirin). No maternal toxicity on offspring were observed in a peri/postnatal toxicity study in rats d at up to 1 mg/kg/day (approximately 0.01 times the maximum recom human 24-hour dose of ribavirin).

Treatment and Posttreatment: Potential Risk to the Fetus

Ribavirin is known to accumulate in intracellular components from wh cleared very slowly. It is not known whether ribavirin is contained in and if so, will exert a potential teratogenic effect upon fertilization of In a study in rats, it was concluded that dominant lethality was not in ribavirin at doses up to 200 mg/kg for 5 days (up to 1.7 times the ma recommended human dose of ribavirin). However, because of the pot human teratogenic effects of ribavirin, male patients should be advise every precaution to avoid risk of pregnancy for their female partners.

COPEGUS should not be used by pregnant women or by men whose f partners are pregnant. Female patients of childbearing potential and patients with female partners of childbearing potential should not rec COPEGUS unless the patient and his/her partner are using effective contraception (two reliable forms) during therapy and for 6 months posttherapy.

To monitor maternal-fetal outcomes of pregnant women exposed to C the COPEGUS Pregnancy Registry has been established. Physicians an are strongly encouraged to register by calling 1-800-526-6367.

Animal Toxicology

Long-term study in the mouse and rat (18-24 months; dose 20-75 an mg/kg/day, respectively (approximately 0.1-0.4 times the maximum daily dose of ribavirin) have demonstrated a relationship between chr ribavirin exposure and an increased incidence of vascular lesions (mic hemorrhages) in mice. In rats, retinal degeneration occurred in contr the incidence was increased in ribavirin-treated rats.

Nursing Mothers

It is not known whether ribavirin is excreted in human milk. Because drugs are excreted in human milk and to avoid any potential for serio adverse reactions in nursing infants from ribavirin, a decision should either to discontinue nursing or therapy with COPEGUS, based on the importance of the therapy to the mother.

Pediatric Use

Safety and effectiveness of COPEGUS have not been established in pa below the age of 18.

Geriatric Use

Clinical studies of COPEGUS and PEGASYS did not include sufficient n subjects aged 65 or over to determine whether they respond differen younger subjects. Specific pharmacokinetic evaluations for ribavirin in elderly have not been performed. The risk of toxic reactions to this dr greater in patients with impaired renal function. COPEGUS should not administered to patients with creatinine clearance <50 mL/min. (see **CLINICAL PHARMACOLOGY** : **Special Populations**).

Effect of Gender

No clinically significant differences in the pharmacokinetics of ribaviri observed between male and female subjects.

(*back to top*)

ADVERSE REACTIONS

PEGASYS in combination with COPEGUS causes a broad variety of ser adverse reactions (see **BOXED WARNING** and **WARNINGS**). In all one or more serious adverse reactions occurred in 10% of patients re PEGASYS in combination with COPEGUS.

The most common life-threatening or fatal events induced or aggrava PEGASYS and COPEGUS were depression, suicide, relapse of drug abuse/overdose, and bacterial infections; each occurred at a frequenc

Nearly all patients in clinical trials experienced one or more adverse e

most commonly reported adverse reactions were psychiatric reactions including depression, irritability, anxiety, and flu-like symptoms such fatigue, pyrexia, myalgia, headache and rigors.

Ten percent of patients receiving 48 weeks of therapy with PEGASYS combination with COPEGUS discontinued therapy. The most common for discontinuation of therapy were psychiatric, flu-like syndrome (eg fatigue, headache), dermatologic and gastrointestinal disorders.

The most common reason for dose modification in patients receiving combination therapy was for laboratory abnormalities; neutropenia (2 thrombocytopenia (4%) for PEGASYS and anemia (22%) for COPEGU

PEGASYS dose was reduced in 12% of patients receiving 1000 mg to COPEGUS for 48 weeks and in 7% of patients receiving 800 mg COPE 24 weeks. COPEGUS dose was reduced in 21% of patients receiving 1 1200 mg COPEGUS for 48 weeks and 12% in patients receiving 800 m COPEGUS for 24 weeks.

Because clinical trials are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinic of a drug cannot be directly compared to rates in the clinical tr another drug. Also, the adverse event rates listed here may no the rates observed in a broader patient population in clinical p

Table 3 Adverse Reactions Occurring in >/=5% of Patients in Hepatitis C Clinical Trials (Study NV15801 *

Body System	PEGASYS 180 µg + 1000 mg or 1200 mg COPEGUS 48 wk	Intron A + 1000 mg or 1200 mg REBETOL® 48 wk
	N=451	N=443
	%	%
Application Site Disorders		
Injection site reaction	23	16
Endocrine Disorders		
Hypothyroidism	4	5
Flu-like Symptoms and Signs		
Fatigue/Asthenia	65	68
Pyrexia	41	55
Rigors	25	37
Pain	10	9
Gastrointestinal		
Nausea/vomiting	25	29
Diarrhea	11	10
Abdominal pain	8	9

Dry mouth	4	7
Dyspepsia	6	5
Hematologic **		
Lymphopenia	14	12
Anemia	11	11
Neutropenia	27	8
Thrombocytopenia	5	<1
Metabolic and Nutritional		
Anorexia	24	26
Weight decrease	10	10
Musculoskeletal, Connective Tissue and Bone		
Myalgia	40	49
Arthralgia	22	23
Back pain	5	5
Neurological		
Headache	43	49
Dizziness (excluding vertigo)	14	14
Memory impairment	6	5
Psychiatric		
Irritability/Anxiety/Nervousness	33	38
Insomnia	30	37
Depression	20	28
Concentration impairment	10	13
Mood alteration	5	6
Resistance Mechanism Disorders		
Overall	12	10
Respiratory, Thoracic and Mediastinal		
Dyspnea	13	14
Cough	10	7
Dyspnea exertional	4	7
Skin and Subcutaneous Tissue		
Alopecia	28	33
Pruritus	19	18
Dermatitis	16	13
Dry Skin	10	13
Rash	8	5
Sweating Increased	6	5
Eczema	5	4
Visual Disorders		
Vision Blurred	5	2

*Described as study 4 in the PEGASYS Package Insert.

**Severe hematologic abnormalities

Patients treated for 24 weeks with PEGASYS and 800 mg COPEGUS w observed to have lower incidence of serious adverse events (3% vs 1 hemoglobin <10 g/dL (3% vs 15%), dose modification of PEGASYS (3 36%) and COPEGUS (19% vs 38%) and of withdrawal from treatmen 15%) compared to patients treated for 48 weeks with PEGASYS and 1 or 1200 mg COPEGUS. On the other hand the overall incidence of adv events appeared to be similar in the two treatment groups.

The most common serious adverse event (3%) was bacterial infection sepsis, osteomyelitis, endocarditis, pyelonephritis, pneumonia). Othe occurred at a frequency of <1% and included: suicide, suicidal ideatio psychosis, aggression, anxiety, drug abuse and drug overdose, angin dysfunction, fatty liver, cholangitis, arrhythmia, diabetes mellitus, au phenomena (eg, hyperthyroidism, hypothyroidism, sarcoidosis, syste erythematosis, rheumatoid arthritis) peripheral neuropathy, aplastic a peptic ulcer, gastrointestinal bleeding, pancreatitis, colitis, corneal ul pulmonary embolism, coma, myositis, and cerebral hemorrhage.

Laboratory Test Values

Anemia due to hemolysis is the most significant toxicity of ribavirin th Anemia (hemoglobin <10 g/dL) was observed in 13% of COPEGUS an PEGASYS combination-treated patients in clinical trials. The maximum hemoglobin occurred during the first 8 weeks of initiation of ribavirin (see **DOSAGE AND ADMINISTRATION** : **Dose Modifications**).

(*back to top*)

OVERDOSAGE

No cases of overdose with COPEGUS have been reported in clinical tri

(*back to top*)

DOSAGE AND ADMINISTRATION

The recommended dose of COPEGUS tablets is provided in Table 4. T recommended duration of treatment for patients previously untreated ribavirin and interferon is 24 to 48 weeks.

The daily dose of COPEGUS is 800 mg to 1200 mg administered orall divided doses. The dose should be individualized to the patient depen baseline disease characteristics (eg, genotype), response to therapy, tolerability of the regimen (see Table 4).

In the pivotal clinical trials, patients were instructed to take COPEGUS food; therefore, patients are advised to take COPEGUS with food.

Table 4 PEGASYS and COPEGUS Dosing Recommendations

Genotype	PEGASYS Dose	COPEGUS Dose	Durati
Genotype 1, 4	180 µg	<75 kg = 1000 mg	48 wee
		>/=75 kg = 1200 mg	48 wee
Genotype 2, 3	180 µg	800 mg	24 wee
Genotypes non-1 showed no increased response to treatment beyond 24 weeks (see Table 2).			
Data on genotypes 5 and 6 are insufficient for dosing recommendations.			

Dose Modifications

If severe adverse reactions or laboratory abnormalities develop durin combination COPEGUS/PEGASYS therapy, the dose should be modifie discontinued, if appropriate, until the adverse reactions abate. If into persists after dose adjustment, COPEGUS/PEGASYS therapy should b discontinued.

COPEGUS should be administered with caution to patients with pre-ex cardiac disease (see Table 5). Patients should be assessed before commencement of therapy and should be appropriately monitored du therapy. If there is any deterioration of cardiovascular status, therapy be stopped (see **WARNINGS**).

Table 5 COPEGUS Dosage Modification Guidelines

Laboratory Values	Reduce Only COPEGUS Dose to 600 mg/day * if:	Discontinu COPEGUS i
Hemoglobin in patients with no cardiac disease	<10 g/dL	<8.5 g/dL
Hemoglobin in patients with history of stable cardiac disease	>/=2 g/dL decrease in hemoglobin during any 4 week period treatment	<12 g/dL desp weeks at redu dose
*One 200 mg tablet in the morning and two 200 mg tablets in the evening.		

Once COPEGUS has been withheld due to either a laboratory abnorma clinical manifestation, an attempt may be made to restart COPEGUS a daily and further increase the dose to 800 mg daily depending upon t physician's judgment. However, it is not recommended that COPEGUS increased to its original assigned dose (1000 mg to 1200 mg).

Renal Impairment

COPEGUS should not be used in patients with creatinine clearance <5 (see **WARNINGS** and **CLINICAL PHARMACOLOGY** : **Special Popu**

(*back to top*)

HOW SUPPLIED

COPEGUS™ (ribavirin) is available as tablets for oral administration. contains 200 mg of ribavirin and is light pink to pink colored, flat, ova film-coated, and engraved with RIB 200 on one side and ROCHE on th side. They are packaged as bottle of 168 tablets (NDC 0004-0086-94

Storage Conditions

Store the COPEGUS Tablets bottle at 25°C (77°F); excursions are per between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]. Keep bottle tightly closed.

REBETRON™ is a trademark of Schering Corporation.

Rx only

Roche Pharmaceuticals

Roche Laboratories Inc.

340 Kingsland Street

Nutley, New Jersey 07110-1199

27897718-1202

Issued: December 2002

Printed in USA

(*back to top*)

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, colo imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufac reproduced in full color by PDR as a quick-reference identification aid every effort has been made to assure accurate reproduction, please r that any visual identification should be considered preliminary. In cas poisoning or suspected overdosage, the drug's identity should be veri chemical analysis.